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REC'D 06 JAN 2005
WIPO PCT

APPLICATION NUMBER: *60/525,347*
FILING DATE: *November 26, 2003*

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17510 U.S. PTO 60/525647 112603

PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

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☒ *Additional inventors are being named on the* 1 *separately numbered sheets attached hereto*

TITLE OF THE INVENTION (280 characters max)

PHOSPHODIESTERASE INHIBITORS

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ENCLOSED APPLICATION PARTS *(check all that apply)*

☒ Specification *Number of Pages* 32
☐ CD(s), Number
☐ Drawing(s) *Number of Sheets*
☐ Other (specify)
☐ Application Data Sheet. See 37 CFR 1.76

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The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.
☒ No.
☐ Yes, the name of the U.S. Government agency and the Government contract number are: ______

Respectfully submitted,

SIGNATURE [signature]

Date 11/26/2003

TYPED or PRINTED NAME G·org E. Heib l

REGISTRATION NO. *(if appropriate)* 42,648

Docket Number: RLL-417PRVUS

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PROVISIONAL APPLICATION COVER SHEET
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PHOSPHODIESTERASE INHIBITORS

Field of the Invention

The present invention relates to isoxazoline derivatives and their analogues, which can be used as phosphodiesterase (PDE) type IV selective inhibitors.

Compounds disclosed herein can be useful in the treatment of AIDS, asthma, arthritis, bronchitis, chronic obstructive pulmonary disease (COPD), psoriasis, allergic rhinitis, shock, atopic dermatitis, Crohn's disease, adult respiratory distress syndrome (ARDS), eosinophilic granuloma, allergic conjunctivitis, osteoarthritis, ulcerative colitis and other inflammatory diseases, especially in humans.

Processes for the preparation of disclosed compounds, pharmaceutical compositions containing the disclosed compounds, and their use as PDE type IV selective inhibitors, are provided.

Background of the Invention

It is known that cyclic adenosine-3',5'-monophosphate (cAMP) exhibits an important role of acting as an intracellular secondary messenger (E.W. Sutherland, and T.W. Roll, Pharmacol.Rev,1960,12, 265). Its intracellular hydrolysis to adenosine 5'-monophosphate (AMP) causes number of inflammatory conditions which are not limited to psoriasis, allergic rhinitis, shock, atopic dermatitis, Crohn's disease, adult respiratory distress syndrome (ARDS), eosinophilic granuloma, allergic conjunctivitis, osteoarthritis, ulcerative colitis. The most important role in the control of cAMP (as well as of cGMP) level is played by cyclic nucleotide phosphodiesterases (PDE) which represent a biochemically and functionally, highly variable superfamily of the enzyme; eight distinct families with more than 15 gene products are currently recognized. Although PDE I, PDE II, PDE III, PDE IV, and PDE VII all use cAMP as a substrate, only PDE IV and PDE VII are highly selective for hydrolysis of cAMP. Inhibitors of PDE, particularly the PDE IV inhibitors, such as rolipram or Ro-1724 are therefore known as cAMP-enhancers. Immune cells contain type IV and type III PDE, the PDE IV type being prevalent in human mononuclear cells. Thus the inhibition of phosphodiesterase type IV has been a target for modulation and, accordingly, for therapeutic intervention in a range of disease processes.

The initial observation that xanthine derivatives, theophylline and caffeine inhibit the hydrolysis of cAMP led to the discovery of the required hydrolytic activity in the cyclic nucleotide phosphodiesterase (PDE) enzymes. More recently, distinct classes of PDE have been recognized (J.A. Bervo and D.H. Reifsnyder, TIPS, 1990,11,150), and their selective inhibition has led to improved drug therapy (C.D. Nicholus, R.A. Challiss and M. Shahid, TIPS, 1991, 12, 19). Thus it was recognized that inhibition of PDE IV could lead to inhibition of inflammatory mediator release (M.W. Verghese et. al, J. Mol. Cell. Cardiol., 1989, 12 (Suppl.II), S 61) and airway smooth muscle relaxation (T. J. Trophy in Directions for new Anti-Asthma Drugs, eds S.R. O Donnell and (G.A.Perssan, 1988, 37, Birkheuserverlag).

U.S. Patent No. 5,686,434 (National stage of WO 95/14680) discloses 3-aryl-2-isoxazolines as anti-inflammatory agents. U.S. Patent Nos. 6,114,367 and 5, 869,511 (National stage of WO 95/24398) disclose isoxazoline compounds as inhibitors of TNF release. WO 95/14681 discloses a series of isoxazoline compounds as anti-inflammatory agents. WO 02/100332 discloses isoxazoline compounds having macrophage inhibitory factor (MIF) antagonist activity.

Summary of the Invention

The present invention provides isoxazoline derivatives and their analogues, which can be used for the treatment of AIDS, asthma, arthritis, bronchitis, chronic obstructive pulmonary disease (COPD), psoriasis, allergic rhinitis, shock, atopic dermatitis, Crohn's disease, adult respiratory distress syndrome (ARDS), eosinophilic granuloma, allergic conjunctivitis, osteoarthritis, ulcerative colitis and other inflammatory diseases. Processes for the synthesis of these compounds are also provided.

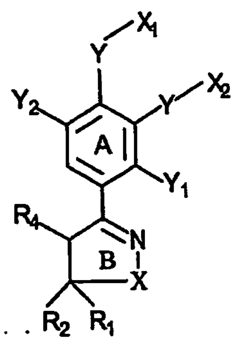
Pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers or N-oxides of these compounds having the same type of activity are also provided.

Pharmaceutical compositions containing the compounds, which may also contain pharmaceutically acceptable carriers or diluents, can be used for the treatment of AIDS, asthma, arthritis, bronchitis, chronic obstructive pulmonary disease (COPD), psoriasis, allergic rhinitis, shock, atopic dermatitis, Crohn's disease, adult respiratory distress syndrome,

eosinophilic granuloma, allergic conjunctivitis, osteoarthritis, ulcerative colitis and other inflammatory diseases.

Other aspects will be set forth in the accompanying description which follows and in part will be apparent from the description or may be learnt by the practice of the invention.

In accordance with one aspect, there are provided compounds having the structure of Formula I:



Formula I

their pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers or N-oxides wherein,

<u>When X is oxygen</u>

R_1 represents hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cyano, nitro, amino, substituted amino, hydroxyl, alkoxy, aryloxy, COR′,

COOR′ (wherein R′ is selected hydrogen, alkyl, alkenyl, alkynyl, (un)saturated cycloalkyl, aryl, aralkyl, heterocyclyl, (heterocyclyl)alkyl, or (heteroaryl)alkyl)

aryl, aralkyl, heteroaryl, heterocyclyl, (heteroaryl) alkyl, (heterocyclyl) alkyl

$(CH_2)_{1\text{-}4}OR'$ (wherein R′ is the same as defined above including hydroxy group),

$C(=O)NR_xR_y$ (wherein R_x and R_y are independently selected from hydrogen, alkyl, alkenyl of three to six carbon atoms, alkynyl of three to six carbon atoms, (un)saturated cycloalkyl, aryl, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl, or heterocyclylalkyl)

$(CH_2)_m$-C(=O)R_3 wherein m is an integer in the range of 0-2 and R_3 can be

-optionally substituted R_p or R_q wherein R_p can be a 4-12 membered (un)saturated monocyclic or bicyclic ring containing 1-4 heteroatom(s) selected from N, O and S wherein the said ring is attached to $(CH_2)_m$C(=O) through N and R_q can be a 4-12 membered (un)saturated monocyclic or bicyclic ring containing 0-4 heteroatom(s) selected from the group consisting of N, O and S wherein the said ring is be attached to $(CH_2)_m$C(=O) through C

wherein the substituents of R_3 are selected from one or more of alkyl, alkenyl, alkynyl,

(un)saturated cycloalkyl, halogen, hydroxyl, alkoxy, aryloxy, nitro, cyano, amino, substituted amino, hydroxyalkyl, oxo, acyl, optionally substituted amino wherein the substituents are selected from C_1-C_6 alkyl, aryl, aralkyl, or cycloalkyl

aryl, carboxyl, alkaryl, carbamoyl, alkyl ether

C(=O)NR_5R_6 (wherein R_5 and R_6 are independently selected from hydrogen

alkyl, alkenyl of three to six carbon atoms, alkynyl of three to six carbon atoms, aryl, and aralkyl)

optionally substituted monocyclic or bicyclic 4-12 membered carbocyclic ring system (wherein the optional substituent(s) is/are selected from alkyl, alkenyl,

alkynyl, halogen, hydroxyl, and alkoxy);

heteroaryl, heterocyclyl, heteroarylalkyl, and heterocyclylalkyl.

R_2 can represent cyano' heteroaryl, heterocyclyl,

$(CH_2)_n$NHCOR_7 (wherein n can be an integer 1 to 6 and R_7 can represent hydrogen, alkyl,

alkenyl, alkynyl, (un)saturated cycloalkyl, alkoxy, aryloxy, aryl, aralkyl, heteroaryl, heterocyclyl $(CH_2)_{1-4}$OR′ (wherein R′ is the same as defined above, and NR_xR_y (wherein R_x and R_y are the same as defined above).

R_4 represents hydrogen, alkyl, halogen, cyano, carboxy, and C(=O)NR_xR_y (wherein R_x and R_y are the same as defined above).

X_1 and X_2 can independently selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalky, acyl, aryl, aralkyl, heteroaryl, heterocyclyl, (heteroaryl)alkyl, and (heterocyclyl)alkyl.

Y can represent oxygen atom, sulphur atom, or

NR (wherein R is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, un(saturated) cycloalkyl, acyl, aryl, aralkyl, heteroaryl, heterocyclyl, (heteroaryl)alkyl, and (heterocyclyl)alkyl).

Y_1 and Y_2 can be independently selected from hydrogen, alkyl, nitro, cyano, halogen, OR (wherein R is the same as defined earlier), SR (wherein R is the same as defined earlier), NHR (wherein R is the same as defined earlier), COOR′, and COR′ (wherein R′ is the same as defined above).

Y_1 and X_2, X_1 and Y_2, X_1 and X_2 may further together form a cyclic ring fused with the ring A containing 3-5 carbon atoms within the ring and having 1-3 heteroatoms selected from N, O and S.

<u>When X is NR_8 or S wherein R_8 is hydrogen, lower alkyl (C_1-C_6) or aryl,</u> and R_1, R_4, X_1, X_2, Y, Y_1 and Y_2 are the same as defined above,

R_2 represents $(CH)_nNHCOR_7$ wherein n represents an integer 1 to 6 and R_7 is the same as defined above,

with the proviso that when R_2 is heterocyclyl, R_1 can not be $(CH_2)_{1\text{-}4}OR'$, $C(=O)NR_xR_y$ or $(CH_2)_m$-$C(=O)R_3$.

The following definitions apply to terms as used herein.

The term "alkyl," unless otherwise specified, refers to a monoradical branched or unbranched saturated hydrocarbon chain having from 1 to 20 carbon atoms. This term is exemplified by groups such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, t-butyl, n-hexyl, n-decyl, tetradecyl, and the like.

Alkyl may further be substituted with one or more substituents selected from the group alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl, acyl, acylamino, acyloxy, amino, aminocarbonyl, alkoxycarbonylamino, azido, cyano, halogen, hydroxy, keto, thiocarbonyl, carboxy, carboxyalkyl, arylthio, thiol, alkylthio, aryloxy, aminosulfonyl,

aminocarbonylamino, hydroxyamino, alkoxyamino, nitro, –SO-alkyl, SO-aryl, -SO-heteroaryl, -SO_2-alkyl, SO_2-aryl and –SO_2-heteroaryl. Unless otherwise constrained by the definition, all substituents may optionally be further substituted by 1-3 substituents chosen from alkyl, carboxy, carboxy-alkyl, aminocarbonyl, hydroxy, alkoxy, halogen, CF_3, amino, substituted amino, cyano, and –$S(O)_nR_9$, where R_9 is alkyl, aryl, or heteroaryl and n is 0, 1 or 2; or an alkyl group as defined above that is interrupted by 1-5 atoms of groups independently chosen from oxygen, sulfur and -NR_a-, where R_a is chosen from hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl. Unless otherwise constrained by the definition, all substituents may optionally be further substituted by 1-3 substituents chosen from alkyl, carboxy, carboxyalkyl, aminocarbonyl, hydroxy, alkoxy, halogen, CF_3, amino, substituted amino, cyano, and –$S(O)_nR_9$, where n and R_9 are the same as defined earlier; or an alkyl group as defined above that has both substituents as defined above and is also interrupted by 1-5 atoms or groups as defined above.

The term "alkenyl," unless otherwise specified, refers to a monoradical of a branched or unbranched unsaturated hydrocarbon group preferably having from 2 to 20 carbon atoms with cis or trans geometry. Particular alkenyl groups include ethenyl or vinyl ($CH=CH_2$), 1-propylene or allyl (-$CH_2CH=CH_2$), iso-propylene (-$C(CH_3)=CH_2$), bicyclo[2.2.1]heptene, and the like. In the event that alkenyl is attached to the heteroatom, the double bond cannot be alpha to the heteroatom.

Alkenyl groups may further be substituted with one or more substituents selected from alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl, acyl, acylamino, acyloxy, amino, aminocarbonyl, alkoxycarbonylamino, azido, cyano, halogen, hydroxy, keto, thiocarbonyl, carboxy, carboxyalkyl, arylthio, thiol, alkylthio, ary, aryloxy, aminosulfonyl, aminocarbonylamino, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-aryl, -SO-heteroaryl, -SO_2-alkyl, SO_2-aryl and –SO_2-heteroaryl. Unless otherwise constrained by the definition, all substituents may optionally be further substituted by 1-3 substituents chosen from alkyl, carboxy, carboxyalkyl, aminocarbonyl, hydroxy, alkoxy, halogen, CF_3, amino, substituted amino, cyano, and –$S(O)_nR_9$, where R_9 is alkyl, aryl, or heteroaryl and n is 0, 1 or 2.

The term "alkynyl," unless and otherwise specified, refers to a monoradical of an unsaturated hydrocarbon, preferably having from 2 to 20 carbon atoms. Particular alkynyl groups include ethynyl, (-C≡CH), propargyl (or propynyl, $-CH_2C{\equiv}CH$), and the like. In the event that alkynyl is attached to the heteroatom, the triple bond cannot be alpha to the heteroatom.

Alkynyl groups may further be substituted with one or more substituents selected from alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl, acyl, acylamino, acyloxy, amino, aminocarbonyl, alkoxycarbonylamino, azido, cyano, halogen, hydroxy, keto, thiocarbonyl, carboxy, carboxyalkyl, arylthio, thiol, alkylthio, aryl, aryloxy, aminosulfonyl, aminocarbonylamino, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-aryl, -SO-heteroaryl, $-SO_2$-alkyl, SO_2-aryl and $-SO_2$-heteroaryl. Unless otherwise constrained by the definition, all substituents may optionally be further substituted by 1-3 substituents chosen from alkyl, carboxy, carboxyalkyl, aminocarbonyl, hydroxy, alkoxy, halogen, CF_3, amino, substituted amino, cyano, and $-S(O)_nR_9$, where R_9 is alkyl, aryl, or heteroaryl and n is 0, 1 or 2.

The term "cycloalkyl" refers to (un)saturated cyclic alkyl groups of from 3 to 20 carbon atoms having a single cyclic ring or multiple condensed rings. Such cycloalkyl groups include, by way of example, single ring structures such as cyclopropyl, cyclobutyl, cyclopentyl, cyclooctyl, cyclopropylene, cyclobutylene and the like, or multiple ring structures such as adamantanyl, and bicyclo [2.2.1]heptane, or cyclic alkyl groups to which is fused an aryl group, for example indane, and the like.

Cycloalkyl groups may further be substituted with one or more substituents selected from alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl, acyl, acylamino, acyloxy, amino, aminocarbonyl, alkoxycarbonylamino, azido, cyano, halogen, hydroxy, keto, thiocarbonyl, carboxy, carboxyalkyl, arylthio, thiol, alkylthio, aryl, aryloxy, aminosulfonyl, aminocarbonylamino, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-aryl, -SO-heteroaryl, $-SO_2$-alkyl, $-SO_2$-aryl and $-SO_2$-heteroaryl. Unless otherwise constrained by the definition, all substituents may optionally be further substituted by 1-3 substituents chosen from alkyl, carboxy, carboxyalkyl, aminocarbonyl, hydroxy, alkoxy, halogen, CF_3, amino,

substituted amino, cyano, and $-S(O)_nR_9$, where R_9 is alkyl, aryl or heteroaryl and n is 0, 1 or 2.

The term "alkoxy" denotes the group O-alkyl wherein alkyl is the same as defined above.

The term "aryloxy" refers to the group O-aryl wherein aryl is the same as defined below.

The term "halogen" refers to fluorine, chlorine, bromine or iodine.

The term "aroyl" stands for CO-aryl wherein aryl is the same as defined below.

The term "aralkyl" refers to $(CH_2)_p$ aryl, wherein p is an integer in the range of 1-6 and aryl is as defined below.

The term "aryl" herein refers to phenyl or naphthyl ring and the like optionally substituted with 1 to 3 substituents selected from halogen, hydroxy, alkyl, alkenyl, alkynyl, cycloalkyl, alkoxy, aryloxy, cyano, nitro, carboxy, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl, C(=O)R″ wherein R″ is selected from the group of hydrogen, alkyl, cycloalkyl, aryl, aralkyl, hydroxy, alkoxy, heteroaryl, heterocyclyl; $(CH_2)_{0\text{-}3}C(=O)NR_xR_y$ wherein R_x and R_y are same as defined earlier.

The term "carboxy" as defined herein refers to $-C(=O)O-R_{10}$ wherein R_{10} is selected from the group hydrogen, alkyl, alkenyl, alkynyl or cycloalkyl

The term "heteroaryl," unless otherwise specified, refers to an aromatic ring structure containing 5 or 6 carbon atoms, or a bicyclic aromatic group having 8 to 10 carbon atoms, with one or more heteroatom(s) independently selected from N, O and S optionally substituted with 1 to 3 substituent(s) selected from halogen, hydroxy, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, alkoxy, aralkyl, cyano, nitro, optionally substituted amino wherein the substituents are selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, aryl; carboxy, -C(=O)R″wherein R″ is the same as defined earlier and $C(=O)NR_xR_y$ wherein R_x and R_y are the same as defined earlier. Examples of heteroaryl groups are pyridinyl, pyridazinyl, pyrimidinyl, pyrrolyl, oxazolyl, thiazolyl, thienyl, isoxazolyl, triazinyl, furanyl, benzofuranyl, indolyl, benzothiazolyl, benzoxazolyl, and the like.

The term 'heterocyclyl," unless otherwise specified, refers to a non-aromatic cycloalkyl group having 5 to 14 atoms in which one or more carbon atom(s) in a ring are replaced by heteroatoms selected from O, S or N, and are optionally benzofused or fused heteroaryl of 5-6 ring members and/or are optionally substituted wherein the substituents are selected from halogen, hydroxy, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, alkoxy, alkaryl, heteroaryl, cyano, nitro, optionally substituted amino wherein the substituents are selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, aryl; carboxy, C(=O)R″ wherein R″ is the same as defined earlier; C(=O)NR$_x$R$_y$ wherein R$_x$ and R$_y$ the same same as defined earlier. One or more carbon(s) of heterocyclyl can also be replaced by carbonyl or thionyl group. Examples of heterocyclyl groups are tetrahydrofuranyl, dihydrofuranyl, dihydropyridinyl, piperidinyl, piperazinyl, dihydrobenzofuryl, dihydroindolyl, and the like.

"Heteroarylalkyl" refers to alkyl-heteroaryl group wherein the alkyl and heteroaryl are the same as defined earlier.

"Heterocyclylalkyl" refers to alkyl-heterocyclyl group wherein the alkyl and heterocyclyl are the same as defined earlier.

The term "acyl" as defined herein refers to -C(=O)R″, wherein R″ is the same as defined earlier.

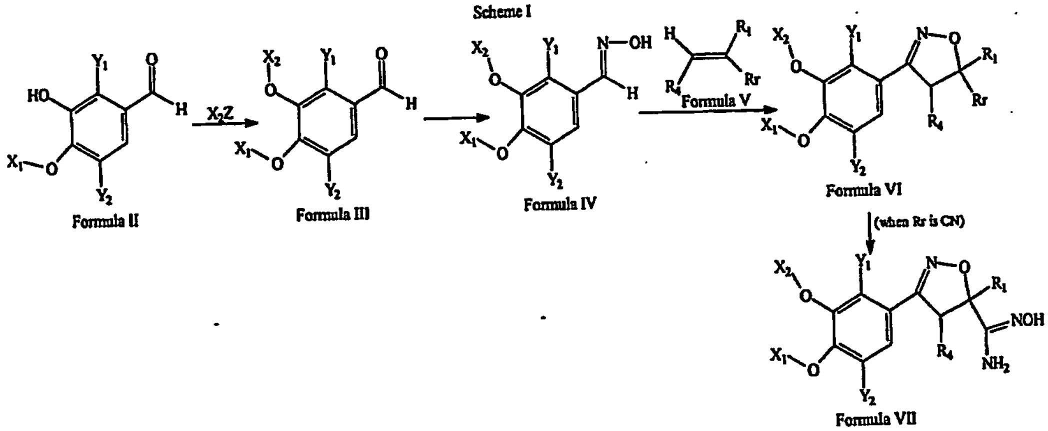
The compounds of the present invention can be used for treating AIDS, asthma, arthritis, bronchitis, chronic obstructive pulmonary disease, psoriasis, allergic rhinitis, shock, atopic dermatitis, Crohn's disease, adult respiratory distress syndrome, eosinophilic granuloma, allergic conjunctivitis, osteoarthritis, ulcerative colitis and other inflammatory diseases.

In accordance with yet another aspect, there are provided processes for the preparation of the compounds as described herein.

Detailed Description of the Invention

The compounds described herein may be prepared by techniques well known in the art and familiar to the average synthetic organic chemist. In addition, the compounds described herein may be prepared by the following illustrative reaction sequences as depicted in Schemes I, IA, IB, II and III.

Scheme I



The compounds of Formula VII can be prepared according to Scheme I. Thus, a compound of Formula II with compound X_2Z (wherein Z is halogen) to give a compound of Formula III [wherein X_1, X_2 (except hydrogen), and Y_1 and Y_2 are the same as defined earlier], which on reaction with hydroxylamine salts, such as the hydrochloride salt, gives a compound of Formula IV, which on treatment with a compound of Formula V gives a compound of Formula VI (wherein R_1 and R_4 are the same as defined earlier and Rr represents CN or $COOCH_3$), which is finally reacted with hydroxylamine salts, such as the hydrochloride salt, (when Rr is CN) to give a compound of Formula VII.

The reaction of a compound of Formula II with a compound X_2Z to give a compound of Formula III can be carried out in a solvent such as tetrahydrofuran, dimethylformamide, dimethylsulphoxide or acetonitrile.

The reaction of a compound of Formula II with compound of formula X_2Z can be carried out in the presence of an inorganic base such as sodium carbonate, sodium bicarbonate, potassium carbonate or potassium bicarbonate.

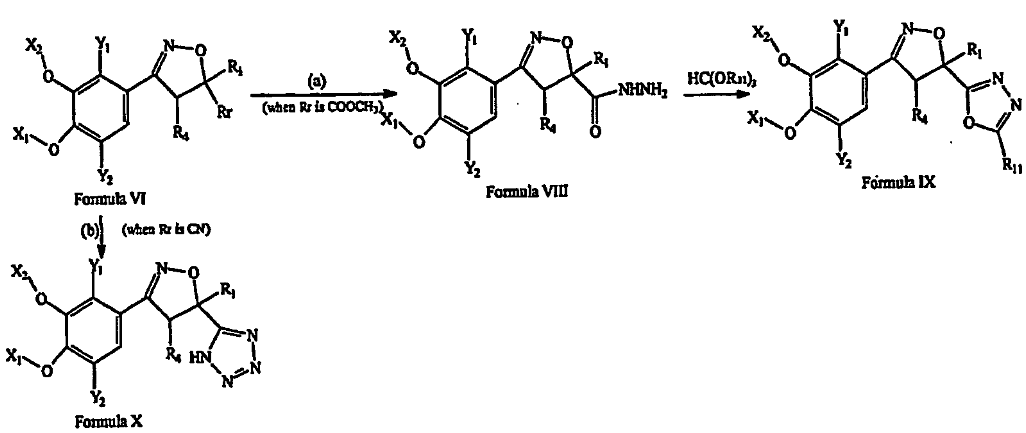
The reaction of a compound of Formula III to give a compound of Formula IV can be carried out in the presence of sodium acetate or potassium acetate in a solvent such as methanol, ethanol, propanol or n-butanol.

The reaction of a compound of Formula IV with a compound of Formula V to give a compound of Formula VI can be carried out in the presence of sodium hypochlorite in a solvent such as tetrahydrofuran, dimethylformamide, dimethylsulphoxide or acetonitrile.

The reaction of a compound of Formula VI with hydroxylamine salts, such as the hydrochloride salt to give a compound of Formula VII can be carried out in a solvent such as tetrahydrofuran, dimethylformamide, dimethylsulphoxide, acetonitrile, acetone, ethanol or mixtures thereof.

The reaction of a compound of Formula VI with hydroxylamine salts, such as the hydrochloride salt, can be carried out in the presence of an inorganic base such as sodium carbonate, sodium bicarbonate, potassium carbonate or potassium bicarbonate.

Scheme IA



The compounds of Formula IX and X can be prepared according to Scheme IA. Thus, reacting a compound of

(a) Formula VI (when Rr is $COOCH_3$) with hydrazine hydrate gives a compound of Formula VIII (wherein X_1, X_2, Y_1, Y_2, R_1 and R_4 are the same as defined earlier), which on reaction with a compound of Formula $HC(OR_{11})_3$ gives a compound of Formula IX (wherein R_{11} represents alkyl from C_1 to C_3); and

(b) Formula VI (when Rr is CN) with sodium azide gives a compound of Formula X (wherein X_1, X_2, Y_1, Y_2, R_1 and R_4 are the same as defined earlier).

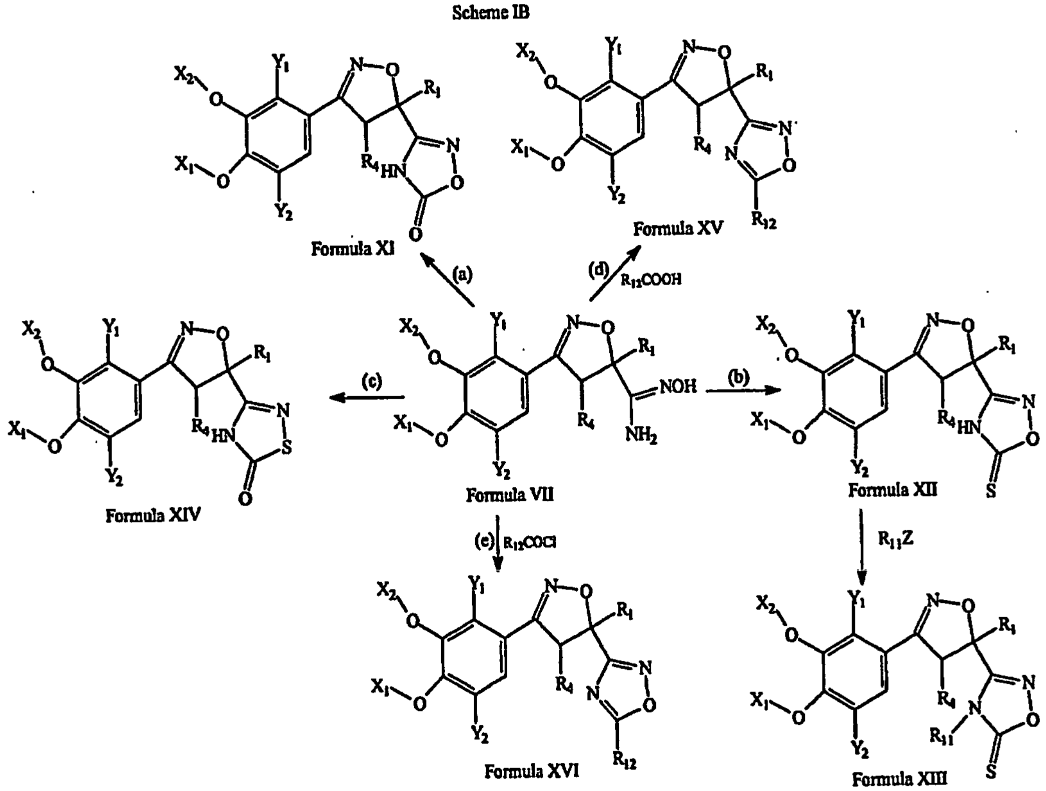
The reaction of a compound of Formula VI with hydrazine hydrate to give a compound of Formula VIII can be carried out at a temperature ranging from about120 to abpit 170^{0}C.

The reaction of a compound of Formula VIII with a compound of Formula $HC(OR_{11})_3$ to give a compound of Formula IX can be carried out at a temperature ranging from about 120 to about 160^{0}C.

The reaction of a compound of Formula VI with sodium azide to give a compound of Formula X can be carried out in a solvent such as benzene, toluene or xylene.

The reaction of a compound of Formula VI with sodium azide to give a compound of Formula X can be carried out in the presence of a mineral acid salt of an organic base such as the hydrochloride salt of trimethylamine, triethylamine or pyridine.

Scheme IB



The compounds of Formulae XI-XVI can be prepared according to Scheme IB. Thus, reacting a compound of Formula VII (wherein X_1, X_2, Y_1, Y_2, R_1 and R_4 are the same as defined earlier) with

(a) methyl chloroformate gives a compound of Formula XI;

(b) thiocarbonyl diimidazole and 1,8-diazabicyclo[5.4.0]undec-7-one gives a compound of Formula XII, which on treatment with a compound of Formula $R_{11}Z$ (wherein Z is halogen) gives a compound of Formula XIII (wherein R_{11} is alkyl);

(c) thiocarbonyl diimidazole and boron trifluoride etherate gives a compound of Formula XIV;

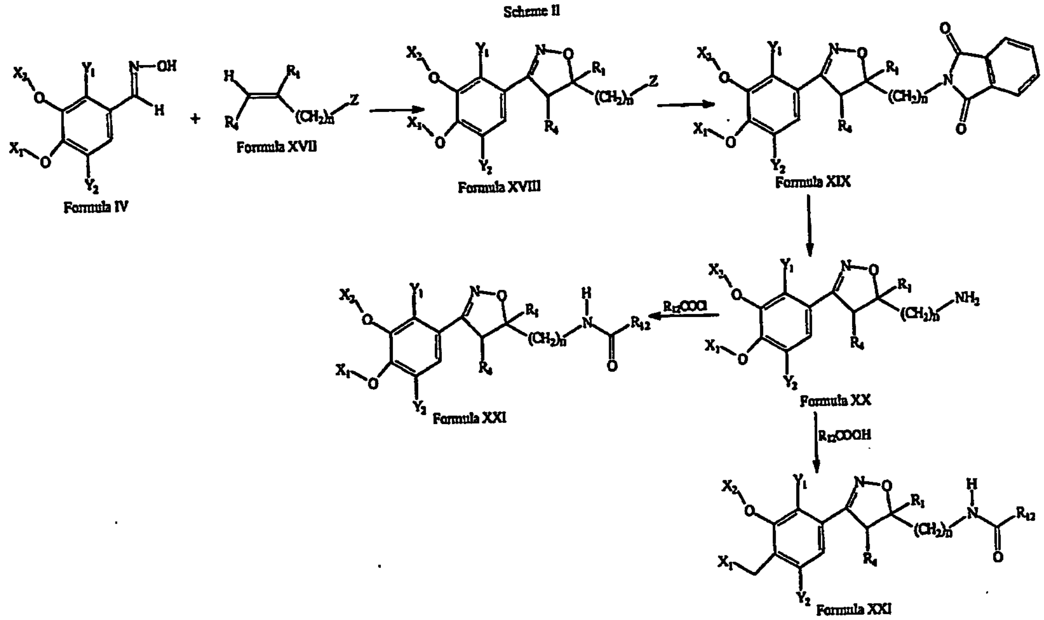
(d) compound of Formula $R_{12}COOH$ to give a compound of Formula XV (wherein R_{12} is alkyl, aryl, heteroaryl or heterocyclyl); and

(e) a compound of Formula $R_{12}COCl$ to give a compound of Formula XVI.

The reaction of a compound of Formula VII with methyl chloroformate to give a compound of Formula XI can be carried out in a solvent such as xylene, benzene or toluene. The reaction of a compound of Formula VII with methyl chloroformate can be carried out in the presence of an organic base such as pyridine, trimethylamine or triethylamine. The reaction of a compound of Formula VII with thiocarbonyl diimidazole and 1,8-diazabicyclo[5.4.0]undec-7-one to give a compound of Formula XII can be carried out in a solvent such as acetonitrile, acetone, dimethylformamide, dimethylsulfoxide or tetrahydrofuran. The reaction of a compound of Formula XII with a compound of Formula $R_{11}Z$ to give a compound of Formula XIII can be carried out in a solvent such as acetone, acetonitrile, tetrahydrofuran or dimethylformamide. The reaction of a compound of Formula XII with a compound of Formula $R_{11}Z$ can be carried out in the presence of an inorganic base such as such as sodium carbonate, sodium bicarbonate, potassium carbonate or potassium bicarbonate. The reaction of a compound of Formula VII with a compound of Formula $R_{12}COOH$ to give a compound of Formula XV can be carried out in the presence of an organic base such as triethylamine, dimethylamine or pyridine.

The reaction of a compound of Formula VII with a compound of Formula $R_{12}COCl$ to give a compound of Formula XVI can be carried out in a solvent such as toluene, acetonitrile, acetone, dimethylformamide, dimethylsulphoxide or tetrahydrofuran.

Scheme II

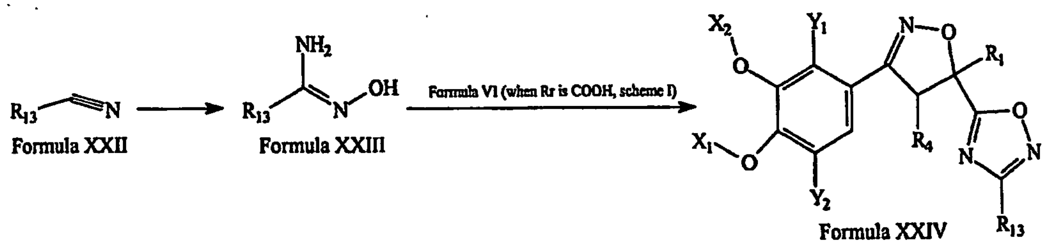


The compounds of Formula XXI can be prepared according to Scheme II. Thus a compound of Formula IV is reacted with a compound of Formula XVII to give a compound of Formula XVIII (wherein X_1, X_2, Y_1, Y_2, R_1, R_4, Z and n are the same as defined earlier), which on treatment with an alkali metal phthalamide, such as potassium phthalamide, gives a compound of Formula XIX, which on treatment with a hydrazine hydrate gives a compound of Formula XX, which is finally treated with a compound of Formula $R_{12}COCl$ or $R_{12}COOH$ to give a compound of Formula XXI (wherein R_{12} is the same as defined earlier).

The reaction of a compound of Formula IV with a compound of Formula XVII to give a compound of Formula XVIII can be carried out in a solvent such as acetonitrile, acetone, dimethylformamide, dimethylsulphoxide or tetrahydrofuran. The reaction of a compound of Formula XVIII with potassium phthalamide to give a compound of Formula XIX can be carried out in a solvent such as acetonitrile, acetone, dimethylformamide, dimethylsulphoxide or tetrahydrofuran. The reaction of a compound of Formula XIX with hydrazine hydrate to give a compound of Formula XX can be carried out in a solvent such as methanol, ethanol, propanol or butanol. The reaction of a compound of Formula XX with a compound of Formula $R_{12}COCl$ to give a compound of Formula XXI can be carried out in a solvent such as chloroform, dichloromethane or dichloroethane. The reaction of a compound of Formula XX

with a compound of Formula $R_{12}COCl$ can be carried out in the presence of an organic base such as trimethylamine, triethylamine or pyridine. The reaction of a compound of Formula XX with a compound of Formula R_8COOH to give a compound of Formula XXI can be carried out in the presence of 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide, 1-hydroxybenzotriazole in a solvent such as dimethylformamide, dimethylsulfoxide or tetrahydrofuran. The reaction of a compound of Formula XX with a compound of Formula $R_{12}COOH$ to give a compound of Formula XXI can be carried out in the presence of an organic base such as N-methyl morpholine, triethylamine or pyridine.

Scheme III



The compounds of Formula XXIV can be prepared according to Scheme III. Thus, a compound of Formula XXII is reacted with a hydroxyl amine hydroxylamine hydrochloride, to give a compound of Formula XXIII (wherein R_{13} is heteroaryl), which on reaction with a compound of Formula VI (when Rr is COOH) gives a compound of Formula XXIV (wherein X_1, X_2, Y_1, Y_2, R_1 and R_4 are the same as defined earlier).

The reaction of a compound of Formula XXII to give a compound of Formula XXIII can be carried out in the presence of sodium carbonate or potassium carbonate in a solvent such as methanol, ethanol, propanol or n-butanol. The reaction of a compound of Formula XXIII with a compound of Formula VI to give a compound of Formula XXIV can be carried out in a solvent such as dimethylformamide or dimethylsulfoxide. The reaction of a compound of Formula XXIII with a compound of Formula VI can be carried out in the presence of an organic base such as triethylamine, trimethylamine or pyridine.

In the above schemes, where the specific solvents, bases, etc., are mentioned, it is to be understood that other solvents, bases etc., known to those skilled in the art may be used. Similarly, the reaction temperature and duration may be adjusted according to the desired needs.

An illustrative list of compounds of the invention are listed below (also shown in Tables 1 and 2)

–3-[3-(3-Cyclopentyloxy-4-methoxyphenyl)-5-methyl-4,5-dihydroisoxazol-5-yl]-4H-[1,2,4]oxadiazol-5-one (Compound No. 1)

–3-[3-(3-Cyclopentyloxy-4-methoxyphenyl)-5-methyl-4,5-dihydroisoxazol-5-yl]-4H-[1,2,4]oxadiazole-5-thione (Compound No. 2)

–3-[3-(3-Cyclopentyloxy-4-methoxyphenyl)-5-methyl-4,5-dihydroisoxazol-5-yl]-4H-[1,2,4]thiadiazol-5-one (Compound No. 3)

–2-[3-(3-Cyclopentyloxy-4-methoxyphenyl)-5-methyl-4,5-dihydroisoxazol-5-yl]-[1,3,4]oxadiazole (Compound No. 4)

–2-[3-(3-Cyclopentyloxy-4-methoxyphenyl)-5-methyl-4,5-dihydroisoxazol-5-yl]-5-methyl-[1,3,4]oxadiazole (Compound No. 5)

–3-[3-(3-Cyclopentyloxy-4-methoxyphenyl)-5-methyl-4,5-dihydroisoxazol-5-yl]-4-methyl-4H-[1,2,4]oxadiazole-5-thione (Compound No. 6)

–3-{3-[3-(3-Cyclopentyloxy-4-methoxyphenyl)-5-methyl-4,5-dihydroisoxazol-5-yl]-[1,2,4]]oxadiazol-5-yl}pyridine (Compound No. 7)

–5-tert-Butyl-3-[3-(3-Cyclopentyloxy-4-methoxyphenyl)-5-methyl-4,5-dihydroisoxazol-5-yl]-[1,2,4]oxadiazole (Compound No. 8)

-5-[3-(3-3-Cyclopentyloxy-4-methoxyphenyl)-5-methyl-4-,5-dihydroisoxazol-5-yl]-1H-tetrazole (Compound No. 9)

-3-(3-Cyclopentyloxy-4-methoxyphenyl)-5-methyl-4-,5-dihydroisoxazole-5-carbonitrile (Compound No. 10)

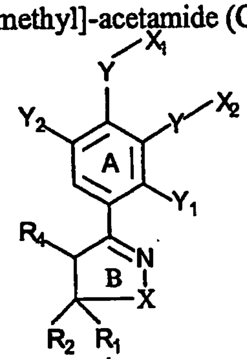
–Morpholine-4-carboxylic acid [3-(3-cyclopentyloxy-4-methoxyphenyl)-5-methyl-4,5-dihydroisoxazol-5-ylmethyl]amide (Compound No. 11)

–N-[3-(3-Cyclopentyloxy-4-methoxyphenyl)-5-methyl-4,5-dihydroisoxazol-5-ylmethyl]-4-fluoro-benzamide (Compound No. 12)

–Adamantane-1-carboxylic acid [3-(3-cyclopentyloxy-4-methoxyphenyl)-5-methyl-4,5-dihydroisoxazol-5-yl-methyl]amide (Compound No. 13)

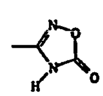
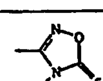
–Furan-2-carboxylic acid [3-(3-cyclopentyloxy-4-methoxyphenyl)-5-methyl-4,5-dihydroisoxazol-5-yl-methyl]amide (Compound No. 14)

–2-(3-Cyclopentyloxy-4-methoxy-phenyl)-N-[3-(3-cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-ylmethyl]-acetamide (Compound No. 15)



Formula I

Table 1: (wherein R_4=Y_1=Y_2=H, R_1=X_1=CH_3, X_2=cyclopentyl, X=Y=O)

Compound No.	R_2
1	
2	

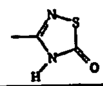
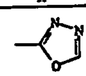
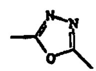
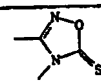
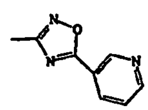
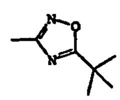
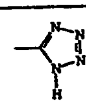
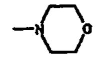
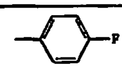
3	
4	
5	
6	
7	
8	
9	
10	CN

Table 2: (Formula I, wherein $R_4=Y_1=Y_2=H$, $R_1=X_1=CH_3$, X_2=cyclopentyl, X=Y=O, $R_2=(CH_2)_n$-NHCO-R_7, n = 1)

Compound no.	R_7
11	
12	
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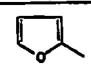
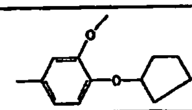
14	
15	

Examples set forth below demonstrate the synthetic procedures for the preparation of some representative compounds. The examples are provided to illustrate particular aspect of the disclosure and do not constrain the scope of the present invention as defined by the claims.

EXAMPLES

Example 1: Preparation of 3-cyclopentyloxy-4-methoxybenzaldehyde

The title compound was prepared according to the method described in J. Med. Chem. (1994), 37, 1696-1703.

Example 2: Preparation of 3-cyclopentyloxy-4-methoxybenzaldehyde oxime

To a stirred solution of 3-cyclopentyloxy-4-methoxybenzaldehyde (0.5g, 2.2727 mmol, Example 1) in ethanol (8ml) was added hydroxylamine hydrochloride(0.473g, 6.8181 mmol) and sodium acetate (0.56 g, 6.8181 mmol). The reaction mixture was allowed to stir at room temperature for 50 minutes. The reaction mixture was then poured in water (20ml) and organic compound was extracted with ethyl acetate (2x15 ml). Ethyl acetate layer was dried over anhydrous sodium sulphate, filtered and finally concentrated under reduced pressure to afford compound of Formula III.

^{1}H NMR ($CDCl_3$): 9.84 (s, 1H), 8.07 (s, 1H), 6.84-7.24 (m, 3H), 4.79-4.83 (m, 1H), 3.87 (s, 3H), 1.62-2.18 (m, 8H).

Example 3: Preparation of [3-(3-Cyclopentyloxy-4-methoxyphenyl)-5-methyl-4,5-dihydroisoxazole-5-carbonitrile (Compound No. 10)

3-cyclopentyloxy-4-methoxybenzaldehyde oxime (500 mg, 0.002 mole, example 2) was taken in 10 mL tetrahydrofuran. Methacrylonitrile (0.285 mL, 0.004 mole) was added and stirred. Sodium hypochlorite solution (10 mL, 20 times) was added dropwise. Reaction mixture was stirred vigorously at an ambient temperature. Tetrahydrofuran was removed under reduced pressure. Water was added and the organic layer was extracted with ethyl acetate, dried and concentrated in vacuo. The residue was purified by column chromatography.

Yield: 63%; m.p.: 105°-106°.

^{1}H NMR: $CDCl_3$ δ= 7.33-7.34 (d, 1H,), 6.96-6.99 (d, 1H,), 6.84-6.87 (d, 1H), 4.80-4.84 (m, 1H,), 3.86-3.88 (s, 3H), 3.80-3.86 (d,1H), 3.36-3.41 (d, 1H), 1.80-2.0 (m, 8H), 1.56-1.63 (s, 3H).

Mass (m/z) 301.5 (M^++1)

Example 4: Preparation of [3-(3-Cyclopentyloxy-4-methoxyphenyl)-N-hydroxy-5-methyl-4,5-dihydroisoxazole-5-carboxamidine

[3-(3-Cyclopentyloxy-4-methoxyphenyl)-5-methyl-4,5-dihydroisoxazole-5-carbonitrile (200 mg, 0.0006 mole, example 3) was dissolved in 5 mL ethanol, and anhydrous potassium carbonate (138 mg, 0.0009 mole) and hydroxylamine hydrochloride (92 mg, 0.0013 mole) were added and the mixture was refluxed. Ethanol was removed under reduced pressure, and water was added. The organic layer was extracted with ethyl acetate, washed with saturated sodium chloride solution, dried and concentrated in vacuo.

Yield : 95%; Mass (m/z): 334.21 (M^++1).

Example 5: Preparation of 3-(3-Cyclopentyloxy-4-methoxyphenyl)-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid hydrazide

To the ester (300 mg, 0.00086 mole, scheme I, Formula VI), hydrazine-hydrate (0.21 mL, 0.0043 mole) was added. The reaction mixture was heated to 120°C. The reaction mixture was cooled, water was added, filtered and dried under vacuum.

Yield : 49%; m.p. : 159-160°.

^{1}H NMR ($CDCl_3$): δ 8.01 (s, 1H), 7.25-7.28 (d, 1H), 6.99-7.02 (d, 1H), 6.81-6.84 (d, 1H), 4.77-4.80 (m, 1H), 3.86 (s, 3H), 3.72-3.80 (d, 1H), 3.20-3.25 (d, 1H), 1.61-2.03 (m, 11H)

Mass (m/z): 334.2 (M^++1)

Example 6: Preparation of 5-[3-(3-3-Cyclopentyloxy-4-methoxyphenyl)-5-methyl-4-,5-dihydroisoxazol-5-yl]-1H-tetrazole (Compound No. 9)

[3-(3-Cyclopentyloxy-4-methoxyphenyl)-5-methyl-4,5-dihydroisoxazole-5-carbonitrile (0.00029 mole, 100 mg, example 3), sodium azide (0.0004 mole) and triethylamine hydrochloride (0.0005 mole, 80 mg) was taken in 20 mL toluene. The reaction mixture was refluxed overnight. Toluene was removed and then added water to it. The mixture was extracted with ethyl acetate, washed with brine, dried and concentrated in vacuo.

Yield : 79%; m.p. : 161°C.

^{1}H NMR (MeOD): δ 7.282-7.288 (d, 1H), 7.11-7.15 (d, 1H), 6.93-6.95 (d, 1H), 4.8 (m, 1H), 3.94-4.0 (d, 1H), 3.81 (s, 3H), 3.61-3.675 (d, 1H), 1.59-1.86 (m, 11H).

Mass (m/z): 344.22 (M^++1)

Example 7: Preparation of 3-[3-(3-Cyclopentyloxy-4-methoxyphenyl)5-methyl-4,5-dihydroisoxazol-5-yl]-4H-[1,2,4]oxadiazole-5-thione (Compound No. 2)

A mixture of [3-(3-Cyclopentyloxy-4-methoxyphenyl)-N-hydroxy-5-methyl-4,5-dihydroisoxazole-5-carboxamidine (0.0006 mole, 200 mg, example 4), thiocarbonyldiimidazole (0.0009 mole, 160 mg) and 1,8-diazabicyclo[5.4.0]undec-7-one

(0.002 mol-358 mL) was taken in acetonitrile and stirred at an ambient temperature. Acetonitrile was removed under reduced pressure, water was added, organic layer was extracted with ethyl acetate, washed with saturated sodium chloride solution, dried and concentrated in vacuo. The residue was purified by column chromatography.

Yield : 50%; m.p : 172°C.

^{1}H NMR ($CDCl_3$): δ 7.26 (d, 1H), 6.98-7.01 (d, 1H), 6.83-6.86 (d, 1H), 4.78-4.81 (m, 1H), 3.88-3.92 (d, 1H), 3.86 (s, 3H), 3.40-3.45 (d, 1H), 1.25-2.04 (m, 11H)

Mass (m/z): 376.15 (M^++1)

Example 8: Preparation of 2-[3-(3-Cyclopentyloxy-4-methoxyphenyl)-5-methyl-4,5-dihydroisoxazol-5-yl]-[1,3,4]oxadiazole (Compound No. 4)

To 3-(3-Cyclopentyloxy-4-methoxyphenyl)-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid hydrazide (250 mg, example 5) was added triethylorthoformate (5 mL). The reaction mixture was heated to 120°C and maintained at that temperature for 3 hours. Excess triethylorthoformate was evaporated and the residue was heated to 140°C and maintained at that temperature for 2 hours. The reaction mixture was diluted with water, saturated with potassium carbonate and extracted with ethyl acetate. The organic layer was dried, concentrated and purified by column chromatography.

Yield : 39%; m.p : 95°C.

^{1}H NMR ($CDCl_3$): δ 8.44 (s, 1H), 7.37 (d, 1H), 7.05-7.08 (d, 1H), 6.85-6.88 (d, 1H), 4.82-4.83 (m, 1H), 4.19-4.24 (d, 1H), 3.88 (s, 3H), 3.43-3.49 (d, 1H), 1.62-2.30 (m, 8H), 1.24-1.28 (s, 3H).

Mass (m/z): 344.16 (M^++1)

Example 9: Preparation of 2-[3-(3-Cyclopentyloxy-4-methoxyphenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-5-methyl-[1,3,4]oxadiazole (Compound No. 5)

Prepared as described in Example 8.

Yield : 75%; m.p : oily.

^{1}H NMR ($CDCl_3$): δ 7.364 (s, 1H), 7.04-7.07 (d, 1H), 6.84-6.87 (d, 1H), 4.816 (s, 1H), 4.16-4.21 (d, 1H), 3.88 (s, 3H), 3.37-3.43 (d, 1H), 2.556 (s, 3H), 1.621-2.15 (m, 8H), 1.25-1.31 (m, 3H)

Mass (m/z) 358.23 (M^++1)

Example 10: Preparation of 3-[3-(3-Cyclopentyloxy-4-methoxyphenyl)-5-methyl-4,5-dihydroisoxazol-5-yl]-4H-[1,2,4]thiadiazol-5-one (Compound No. 3)

Amidoxime (200 mg, 0.0006 mole, Scheme I, Formula VII) was taken in 3 mL tetrahydrofuran, and thiocarbonyl diimidazole (160 mg, 0.0007 mole) was added. Reaction mixture was stirred at an ambient temperature. The reaction mixture was diluted with water, extracted with ethyl acetate, washed with water, dried and concentrated in vacuo. The residue was dissolved in tetrahydrofuran. Boron trifluoride etherate (0.003 mol) was added dropwise. The reaction mixture was stirred at an ambient temperature for 2 hours, diluted with water, extracted with ethyl acetate, dried, concentrated in vacuo and purified by column chromatography.

Yield : 23%; m.pt : 204°C,

^{1}H NMR ($CDCl_3$): δ 7.319 (s, 1H), 7.015-7.042 (d, 1H), 6.83.6.85 (d, 1H), 4.80-4.82 (m, 1H), 3.95-4.00 (d, 1H), 3.87 (s, 3H), 3.33-3.39 (d, 1H), 1.83-2.04 (m, 8H), 1.25-1.62 (m, 3H).

Mass (m/z): 376.14 (M^++1)

Example 11: Preparation of 3-[3-(3-Cyclopentyloxy-4-methoxyphenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-4H-[1,2,4]oxadiazol-5-one (Compound No. 1)

Amidoxime (100 mg, 0.0003 mole, Scheme I, Formula VII) was taken in dimethylformamide (1 mL). At 0^0C pyridine was added, then at same temperature, ethylchloroformate was added dropwise. The reaction mixture was stirred, water was added and organic layer was extracted with ethyl acetate, washed with saturated sodium chloride solution, dried and concentrated in vacuo. Xylene was added to the residue and refluxed for

18 hours. Xylene was removed under reduced pressure. The crude product was purified by column chromatography.

Yield : 37%; m.pt. : oily.

^{1}H NMR ($CDCl_3$): δ 7.29 (s, 1H), 7.01-7.04 (d, 1H), 6.84-6.87 (d, 1H), 4.78-4.81 (m, 2H), 3.91-3.96 (d, 1H), 3.88 (s, 3H), 3.31-3.40 (d, 1H), 1.22-2.00 (m, 11H)

Mass (m/z): 360.18 (M^++1)

Example 12: Preparation of 3-{3-[3-(3-Cyclopentyloxy-4-methoxyphenyl)-5-methyl-4,5-dihydroisoxazol-5-yl]-[1,2,4]loxadiazol-5-yl}-pyridine (Compound No. 7)

Nicotinic acid (0.0002 mole, 30 mg) was dissolved in dry dimethylformamide (1 mL), and molecular sieves (100 mg, 4 A°) and triethylamine (0.0003 mole, .05 mL) were added. The reaction mixture was cooled to -20°C and isobutylchloroformate (0.0004 mole, .06 mL) were added. After 10 minutes amidoxime (0.0004 mole, 160 mg, Scheme I, Formula VII) in dimethylformamide (2 mL) were added. The reaction mixture was stirred at an ambient temperature overnight. Some fresh molecular sieves were added. The reaction mixture was heated at 120°C for 12 hours, and the mixture was filtered. To the filtrate, water was added, extracted with ethyl acetate, washed, dried and concentrated in vacuo. The residue was purified by column chromatography.

Yield : 25%; m.p. : oily.

^{1}H NMR ($CDCl_3$): δ 9.38 (s, 1H), 8.83-8.84 (d, 1H), 8.42-8.44 (d, 1H), 7.47-7.51 (m, 2H), 7.06-7.09 (d, 1H), 6.85-6.87 (d, 1H), 4.81-4.83 (m, 1H), 4..07-4.13 (d, 1H), 3.88 (s, 3H), 3.41-3.46 (d, 1H), 1.62-2.09 (m, 8H), 0.8-0.98 (m, 3H).

Mass (m/z): 421.40 (M^++1)

Example 13: Preparation of 5-tert-Butyl-3-[3-(3-Cyclopentyloxy-4-methoxyphenyl)-5-methyl-4,5-dihydroisoxazol-5-yl]-[1,2,4]oxadiazole (Compound No. 8)

Amidoxime (100 mg, 0.0003 mole, scheme I, Formula VII) was taken in benzene (2 mL) and pivaloyl chloride (0.1 mL, 0.0009 mole) was added. The reaction mixture was refluxed. Benzene was removed under reduced pressure. The residue was dissolved in ethyl acetate, washed with saturated sodium bicarbonate solution, dried and concentrated in vacuo. The residue was taken in dimethylformamide (5 mL) and refluxed for 3 hours. Dimethylformamide was removed under reduced pressure, water was added, extracted with ethyl acetate, dried and concentrated in vacuo.

Yield : 25%; m.p. : sticky solid.

^{1}H NMR (CDCl$_3$): δ 7.39-7.40 (d, 1H), 7.04-7.08(d, 1H), 6.84-6.87 (d, 1H), 4.80-4.83 (m, 1H), 4.02-4.07 (d, 1H), 3.87 (s, 3H), 3.31-3.36 (d, 1H), 1.74-1.96 (m, 8H), 1.43 (s, 9H), 1.24-1.35 (m, 3H).

Mass (m/z): 400.42 (M^++1)

Example 14: Preparation of 3-[3-(3-Cyclopentyloxy-4-methoxyphenyl)-5-methyl-4,5-dihydroisoxazol-5-yl]-4-methyl-4H-[1,2,4]oxadiazole-5-thione (Compound No. 6)

3-[3-(3-Cyclopentyloxy-4-methoxyphenyl)-5-methyl-4,5-dihydroisoxazol-5-yl]-4H-[1,2,4]oxadiazole-5-thione (0.0001 mole, 40 mg, example 7), was dissolved in acetone (2 mL). To it potassium carbonate (0.001 mole, 147 mg) and methyliodide (0.0002 mole, .016 mL) were added. The reaction mixture was refluxed overnight, filtered to remove potassium carbonate, and washed with acetone. From the filtrate, acetone was removed under reduced pressure to give a low melting solid compound.

Yield : 72%

^{1}H NMR (CDCl$_3$): δ 7.38 (d, 1H), 7.03-7.06 (d, 1H), 6.83-6.86 (d, 1H), 4.80-4.82 (m, 1H), 3.97-4.02 (d, 1H), 3.87 (s, 3H), 3.31-3.37 (d, 1H), 2.72 (s, 3H), 1.80-1.99 (m, 8H), 1.26-1.32 (m, 3H).

Mass (m/z): 390.38 (M^++1)

Example 15: General method of preparation of compound of Formula XXI (wherein $R_1=X_1=CH_3$, $Y_1=R_4=Y_2=H$, X_2=cyclopentyl and n=1)

Method A: To a stirred solution of 3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-methylamine (0.3569 mmol, 1equiv, Scheme II, Formula XX) in 2 mL chloroform was added triethylamine (2.6767 mmol, 7.5 equiv). The compound of Formula $R_{12}COCl$ (0.3925 mmol, 1.1equiv) was added dropwise over a period of 15 minutes with vigorously stirring at an ambient temperature. The reaction mixture was quenched by adding 5 mL water. The resulting mixture was extracted with chloroform. The organic layer was thoroughly washed with water and was dried over anhydrous sodium sulphate, filtered and concentrated over a rotary evaporator to afford the crude product. The crude product was purified over silica gel column (100-200 mesh) using hexane and ethyl acetate mixture as eluent.

The following compounds were prepared following the above general procedure

–Morpholine-4-carboxylic acid [3-(3-cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-ylmethyl]-amide (Compound No. 11)

–N-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-ylmethyl]-4-fluoro-benzamide (Compound No. 12)

–Adamantane-1-carboxylic acid [3-(3-cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl-methyl]amide (Compound No. 13)

–Furan-2-carboxylic acid [3-(3-cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-ylmethyl]-amide (Compound No. 14)

Method B: To a solution of 3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-methylamine (0.3407 mmol, 1 equiv, Scheme II, Formula XX) and $R_{12}COOH$ (0.3407 mmol, 1 equiv.) in 0.8 mL dry dimethylformamide at $0^{0}C$ was added 1-hydroxybenzotriazole (0.3407 mmol, 1 equiv) and N-methylmorpholine (1.3628 mmol, 4 equiv.). The reaction mixture was allowed to stir at 0 ^{0}C for 30 minutes. Thereafter, 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide (0.6814 mmol, 2 equiv.) was added to the reaction mixture and reaction was continued at 0 ^{0}C for 1 hour and therafter at an ambient temperature for 20 hours. The reaction was quenched by adding water. The resulting reaction mixture was

extracted with ethyl acetate. The ethyl acetate layer was dried over anhydrous sodium sulphate, concentrated over a rotary evaporator to afford the crude product. The crude product was purified over silica gel column (100-200 mesh) using hexane and ethyl acetate mixture as eluent.

The following compound was prepared following the above procedure (Method B)

–2-(3-Cyclopentyloxy-4-methoxy-phenyl)-N-[3-(3-cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-ylmethyl]-acetamide (Compound No. 15)

Example 16: Efficacy of compounds as PDE IV inhibitors

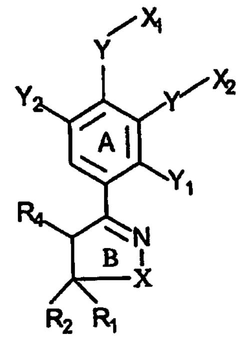
PDE-IV Enzyme Assay

The efficacy of compounds of PDE-4 inhibitors is determined by an enzyme assay using U937 cell cytosolic fraction (BBRC, 197: 1126-1131, 1993). Hydrolysis of cAMP to AMP was monitored using HPLC and [^{3}H]cAMP in the sample was detected using FLO-ONE Detector.

The enzyme preparation is incubated in the presence and absence of the test compound for 30 min and amount of [^{3}H]cAMP measured in the sample. The IC_{50} values were found to be in the range of nM to μM concentration.

We claim:

1. Compounds having the structure of Formula I:



Formula I

their pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers or N-oxides wherein,

a) When X is oxygen;

R_1 represents hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cyano, nitro, amino, substituted amino, hydroxyl, alkoxy, aryloxy, COR′, COOR′ (wherein R′ is selected hydrogen, alkyl, alkenyl, alkynyl, (un)saturated cycloalkyl, aryl, aralkyl, heterocyclyl, (heterocyclyl)alkyl, or (heteroaryl)alkyl) aryl, aralkyl, heteroaryl, heterocyclyl, (heteroaryl) alkyl, or (heterocyclyl) alkyl, $(CH_2)_{1\text{-}4}OR'$ (wherein R′ is the same as defined above including hydroxy group), $C(=O)NR_xR_y$ (wherein R_x and R_y are independently selected from hydrogen, alkyl, alkenyl of three to six carbon atoms, alkynyl of three to six carbon atoms, (un)saturated cycloalkyl, aryl, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl, or heterocyclylalkyl), $(CH_2)_m\text{-}C(=O)R_3$ (wherein m is an integer in the range of 0-2 and R_3 represents

- optionally substituted R_p or R_q wherein R_p represents a 4-12 membered (un)saturated monocyclic or bicyclic ring containing 1-4 heteroatom(s) selected from N, O and S wherein the said ring is attached to $(CH_2)_mC(=O)$ through N and R_q represents a 4-12 membered (un)saturated monocyclic or bicyclic ring containing 0-4 heteroatom(s) selected from the group consisting of N, O and S wherein the said ring is be attached to $(CH_2)_mC(=O)$ through C,

wherein the substituents of R_3 are selected from one or more of alkyl, alkenyl, alkynyl, (un)saturated cycloalkyl, halogen, hydroxyl, alkoxy, aryloxy, nitro, cyano, amino, substituted amino, hydroxyalkyl, oxo, acyl, optionally substituted amino wherein the substituents are selected from C_1-C_6 alkyl, aryl, aralkyl, or cycloalkyl; aryl, carboxyl, alkaryl, carbamoyl, alkyl ether, $C(=O)NR_5R_6$ (wherein R_5 and R_6 are independently selected from hydrogen, alkyl, alkenyl of three to six carbon atoms, alkynyl of three to six carbon atoms, aryl, and aralkyl), optionally substituted monocyclic or bicyclic 4-12 membered carbocyclic ring system (wherein the optional substituent(s) is/are selected from alkyl, alkenyl, alkynyl, halogen, hydroxyl, and alkoxy), heteroaryl, heterocyclyl, heteroarylalkyl, and heterocyclylalkyl;

R_2 represents cyano' heteroaryl, heterocyclyl, $(CH_2)_nNHCOR_7$ (wherein n represents an integer 1 to 6 and R_7 represents hydrogen, alkyl, alkenyl, alkynyl, (un)saturated cycloalkyl, alkoxy, aryloxy, aryl, aralkyl, heteroaryl, heterocyclyl $(CH_2)_{1-4}OR'$ (wherein R′ is the same as defined above, and NR_xR_y (wherein R_x and R_y are the same as defined above);

R_4 represents hydrogen, alkyl, halogen, cyano, carboxy, and $C(=O)NR_xR_y$ (wherein R_x and R_y are the same as defined above); X_1 and X_2 are independently selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalky, acyl, aryl, aralkyl, heteroaryl, heterocyclyl, (heteroaryl)alkyl, and (heterocyclyl)alkyl;

Y represents oxygen atom, sulphur atom, or NR (wherein R is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, un(saturated) cycloalkyl, acyl, aryl, aralkyl, heteroaryl, heterocyclyl, (heteroaryl)alkyl, and (heterocyclyl)alkyl);

Y_1 and Y_2 represents independently selected from hydrogen, alkyl, nitro, cyano, halogen, OR (wherein R is the same as defined earlier), SR (wherein R is the same as defined earlier), NHR (wherein R is the same as defined earlier), COOR′, and COR′ (wherein R′ is the same as defined above); Y_1 and X_2, X_1 and Y_2, X_1 and X_2 may further together form a cyclic ring fused with the ring A containing 3-5 carbon atoms within the ring and having 1-3 heteroatoms selected from N, O and S; and

b) When X is NR_8 or S wherein R_8 is hydrogen, lower alkyl (C_1-C_6) or aryl, and R_1, R_4, X_1, X_2, Y, Y_1 and Y_2 are the same as defined above,

R_2 represents $(CH)_nNHCOR_7$ wherein n represents an integer 1 to 6 and R_7 is the same as defined above, with the proviso that when R_2 is heterocyclyl, R_1 can not be $(CH_2)_{1-4}OR'$, $C(=O)NR_xR_y$ or $(CH_2)_m$-$C(=O)R_3$.

Abstract

The present invention relates to isoxazoline derivatives and their analogues, which can be used as phosphodiesterase (PDE) type IV selective inhibitors. Compounds disclosed herein can be useful in the treatment of AIDS, asthma, arthritis, bronchitis, chronic obstructive pulmonary disease (COPD), psoriasis, allergic rhinitis, shock, atopic dermatitis, Crohn's disease, adult respiratory distress syndrome (ARDS), eosinophilic granuloma, allergic conjunctivitis, osteoarthritis, ulcerative colitis and other inflammatory diseases, especially in humans. Processes for the preparation of disclosed compounds, pharmaceutical compositions containing the disclosed compounds, and their use as PDE type IV selective inhibitors, are provided.

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